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Long Covid: does it exist? What is it? We can we do for sufferers?

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Long Covid: does it exist? What is it? We can we do for sufferers?

Commentary

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As we gradually work our way out of the Covid-19 pandemic in the United States thanks to vaccinations, we will hopefully see many fewer desperately ill patients on ventilators and fewer deaths. Looming over the profession is the large and growing numbers of people with what has been termed "long Covid:" patients who have recovered from their acute illness who present with many persistent complaints. There is still considerable confusion about this entity. There is vigorous debate over whether this is a "real" entity with a biologic basis or whether it is psychosomatic. The NIH has announced plans to support research into long Covid, but patients are presenting to their physicians now and seeking help.

There are two relatively distinct forms that "long Covid" can take: persisting symptoms in those who were seriously ill and new symptoms in those, often younger people, who had only mild or even no symptoms with their acute infection.

It is not surprising that very sick Covid-19 survivors have symptoms that persist long after they are discharged from hospital. In recent years increased attention has been paid to the Post-ICU

syndrome (1,2). A prolonged ICU stay is often followed by persistent cognitive dysfunction, muscle weakness and intrusive memories similar to those seen with post-traumatic stress disorder.

Hospitalized Covid-19 patients with critical or severe illness were studied at discharge. 77% were below the 2.5th percentile in functional capacity assessed by the one-minute sit-to-stand test and 15 of 48 had oxygen desaturation. After three months only one patient had a result above the 50th percentile (3). Swedish investigators found that more than half of ICU-treated Covid-19 survivors had impaired CO diffusing capacity at four months post discharge (4). In France, 478 patients discharged from hospital were interviewed by telephone at four months after discharge. 51% reported at least one symptom that had not existed before their illness. The most common were fatigue in 31%, cognitive impairment in 21% and dyspnea in 16%. Lung CT was done in 171 patients and 63% had abnormalities, mostly subtle ground-glass opacities. In Italy, 143 previously hospitalized patients were assessed at a mean of 60.3 days after onset of symptoms. Only 18 (12.6%) were asymptomatic. The most commonly reported symptoms were fatigue (53%), dyspnea (43.4%, joint pain (27.3%) and chest pain (21.7%) (6).

These patients can often be assured that their symptoms should improve with time and seem to be helped by an active rehab program (3).

Much more challenging are the patients whose initial infection was mild or even asymptomatic. Swedish investigators compared a group of health care professionals who were seropositive for SARS-CoV-2 at enrollment and who reported no or mild antecedent symptoms with seronegative patients at eight months after testing (7). Most symptoms were mild, but 26% of seropositive subjects reported at least one moderate to severe symptom for at least 2 months compared to 9% of seronegative subjects. Mexican investigators studied 115 patients with mostly mild to moderate PCR-confirmed Covid-19 at least 30 days after symptom onset. Four were sick enough to require ICU care. There was a severe decrease in quality of life in 56% (8).

The University of Washington followed 177 patients with documented Covid-19, of whom 16 were admitted to hospital and 150 were treated as outpatients; 64% of the latter group sought no care after diagnosis. Of the outpatients contacted a mean of 169 days after symptom onset, 31% had one or more persisting symptoms (9).

Patients' symptoms after mild Covid-19 include anosmia, fatigue, palpitations, insomnia, hyperhidrosis, dysgeusia, "brain fog" and dyspnea (6-10).

It is easy for physicians to attribute symptoms to anxiety, but this is neither helpful to our patients nor necessarily true. "Hard" neurologic illnesses, including ischemic strokes and intracranial hemorrhage have been found to be more common in patients recovered from even mild Covid-19 (11). Certainly the two leading hypotheses as to the cause of "long-Covid" are psychosomatic and immune-mediated, but persisting small vessel thrombi have also been postulated.

Pending the results of larger controlled studies, what can we offer our patients? While anecdotal at this point, many patients with persisting symptoms after a mild/asymptomatic infection have reported improvement in symptoms after vaccination. Since these patients are still at risk for reinfection, advising vaccination is appropriate whether or not it helps their symptoms. Critically, we should not dismiss their complaints as being "all in their head." This may be wrong, and even if correct is not helpful. It is appropriate to acknowledge their distress, get those with fatigue and/or dyspnea in a structured exercise program, and work with all on symptomatic relief.

References:

1. Myers EA, Smith DA, Allen SR, Kaplan LJ. *Post-ICU syndrome: Rescuing the undiagnosed.* JAAPA 2016 Apr;29(4):34-7
2. Svenningsen H, Langhorn L, Agard AS, Dreyer P. *Post-ICU symptoms, consequences and follow-up: an integrative review.* Nurs Crit Care 2017 Jul;22(4):212-220
3. Martin I, Braem F, Baudet L et al. *Follow-up of functional exercise capacity in patients with Covid-19: it is improved by telerehabilitation.* Resp Med 2021 epub ahead of print. https://doi.org/10.1016/j.rmed2021.106438
4. Ekbom E, Frithiof R, Emilsson OI et al. *Impaired diffusing capacity for carbon monoxide is common in critically ill Covid-19 patienst at four months post-discharge.* Resp Med 2021 epub ahead of print. https:/doi.org/10.1016/j.rmed.2021.106394
5. The Writing Committee for the COMEBAC Study Group. *Four-month clinical status of a cohort of patients after hospitalization for Covid-19.* JAMA 2021:325(15):1525-1534
6. Carfi A, Bernabei R, Landi F et al. *Persistent symptoms in patients after acute Covid-19.* JAMA 2020;324(6):603-605
7. Havervall S, Rosell A, Phillipson M et al. *Symptoms and functional impairment assess 8 months after mild Covid-19 among health care workers.* JAMA 2021 Apr 7;e215612. doi: 10.1001/jama.2021.5612. Online ahead of print
8. Ordinola Navarro AO, Cervantes-Bojalil J, Quevedo O deJ C et al. *Decreased quality of life and spirometric alterations even after mild-moderate Covid-19.* Respir Med. 2021 Apr 14;181:106391. doi: 10.1016/j.rmed.2021.106391. Online ahead of print.
9. Logue JK, Franko NM, McCulloch DJ et al. *Sequelae in adults at 6 months after Covid-19 infection.* JAMA Network Open 2021;4(2):e210830
10. Huang Y, Pinto MD, Borelli JL et al. *COVID symptoms, symptom clusters and predictors for becoming a long-hauler.* medRxiv. 2021 Mar 5:2021.03.03.21252086. doi: 10.1101/2021.03.03.21252086. Preprint
11. Taquet M, Geddes JR, Husain M et al. *6-month neurologic and psychiatric outcomes in 236,379 survivors of Covid-19: a retrospective cohort study using electronic health records.* Lancet Psychiatry 2021 May;8(5):416-427